

This is a repository copy of *"The legacy of thalidomide" - A multidisciplinary meeting held at the University of York, United Kingdom, on September 30, 2016 : A multidisciplinary meeting held at the University of York, UK on September 30, 2016.*

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/112419/>

Version: Accepted Version

Article:

Newbronner, Elizabeth orcid.org/0000-0003-2366-9981, Vargesson, Neil and Atkin, Karl orcid.org/0000-0003-1070-8670 (2017) "The legacy of thalidomide" - A multidisciplinary meeting held at the University of York, United Kingdom, on September 30, 2016 : A multidisciplinary meeting held at the University of York, UK on September 30, 2016. Birth Defects Research Part A: Clinical and Molecular Teratology. pp. 296-299. ISSN 1542-0760

<https://doi.org/10.1002/bdra.23619>

Reuse

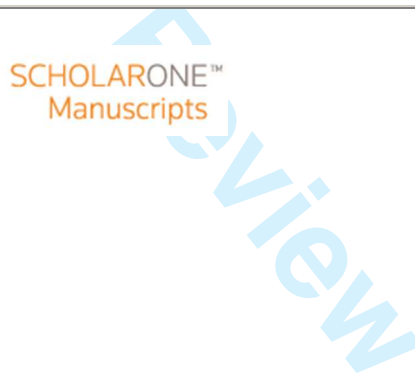
Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

**'The Legacy of Thalidomide' - a multidisciplinary Meeting
held at the University of York, UK on September 30, 2016.**

Journal:	<i>Birth Defects Research</i>
Manuscript ID	Draft
Wiley - Manuscript type:	Brief Report
Date Submitted by the Author:	n/a
Complete List of Authors:	Newbronner, Elizabeth; University of York, Department of Health Sciences, Faculty of Sciences. Area 2 Seebohn Rowntree Building Vargesson, Neil; University of Aberdeen, School of Medicine, Medical Sciences & Nutrition. Institute of Medical Sciences. Foresterhill. Atkin, Karl; University of York, Department of Health Sciences, Faculty of Sciences. Area 2 Seebohn Rowntree Building
Key Words:	Thalidomide, Thalidomide Society, Thalidomide Trust, Wellcome Library, Global Health History, Drug safety, Aging with early onset disability, Mechanism of action, Thalidomide Survivors



Brief Report

'The Legacy of Thalidomide' - a multidisciplinary Meeting held at the University of York, UK on September 30, 2016.

Elizabeth Newbronner¹, Neil Vargesson^{2,*} and Karl Atkin¹

1. Department of Health Sciences. Faculty of Sciences. University of York. Area 2 Seebohm Rowntree Building. Heslington. York. YO10 5DD.

2. School of Medicine, Medical Sciences and Nutrition, Institute of Medical Sciences. University of Aberdeen. Foresterhill. Aberdeen. AB25 2ZD.

* Corresponding Author: Dr Neil Vargesson. Email: n.vargesson@abdn.ac.uk. Tel: 01224 437374.

Keywords: Thalidomide, Thalidomide Survivors, Thalidomide Society, Thalidomide Trust, Wellcome Library, Global Health History, aging with early onset disability, drug safety

Abstract

Background

Between 1957-1962 thalidomide was used as a non-addictive, non-barbiturate sedative that also was successful in relieving the symptoms of morning sickness in early pregnancy. Infamously, thousands of babies were subsequently born with severe birth defects. The drug is used again, today, to successfully treat leprosy, and tragically, there is a new generation of thalidomide damaged children in Brazil. While the outward damage in babies has been documented, the effects of the damage upon the survivors as they grow up, the lifestyle changes and adaptations required to be made, as well as studies into ageing in survivors, has received little attention and remains understudied.

Methods/Results

A unique multidisciplinary meeting was organised at the University of York bringing together thalidomide survivors, clinicians, scientists, historians and social scientists to discuss the past, the current and the future implications of thalidomide.

Conclusions

There is still much to learn from thalidomide, from its complex history and ongoing impact on peoples' lives today, to understanding its mechanism/s to aid future drug safety, to help identify new drugs retaining clinical benefit without the risk of causing embryopathy. For thalidomide survivors, the original impairments caused by the drug are compounded by the consequences of a lifetime of living with a rare disability, and early on-set age related health problems. This has profound implications for their quality of life and need for health and social care services. It is vital that these issues are addressed in research, and in clinical practice if thalidomide survivors are to 'age well'.

Background

Landmark papers in The Lancet by Dr William McBride (McBride, 1961) and Dr Widikund Lenz (Lenz, 1962) first drew the medical world’s attention to Thalidomide and the extensive damage the drug caused to babies when their mother took it to combat morning sickness in early pregnancy. In the immediate aftermath, much was written about the health of babies affected, the teratogenic effects of the drug and the scientific and legal implications of the ‘Thalidomide disaster’ (Smithells and Newman, 1992). Given the drug is now used around the world again to successfully treat conditions like leprosy in Brazil, in 2014 a World Health Organisation sponsored meeting of experts (World Health Organisation, 2014; www.who-umc.org/graphics/28280.pdf) reexamined the diagnostic criteria of Thalidomide embryopathy and the mechanisms of causation (Vargesson, 2015). This was in response to a new generation of thalidomide damaged children being seen in Brazil (Schuler-Facini et al., 2007; Vianna et al., 2011; Vargesson, 2013). Yet, the effects of the damage upon the survivors as they grow up, has only recently started to be studied. It is really in the past decade, as Thalidomide survivors reached their 50’s, there has been renewed interest in their health and in particular the effects of ageing with Thalidomide embryopathy. In November 2015, a symposium organised by the University of Tokyo focused on clinicians conducting research into ageing and early onset age-related effects in people with Thalidomide embryopathy (Honoshita, 2015).

However, the issues, both practical and clinical, affecting the day-to-day life of Thalidomide survivors have rarely been discussed. In addition an understanding of the long-term consequences of thalidomide embryopathy in survivors remains understudied. A recent meeting in September 2016 organised by Ms Elizabeth Newbronner and Prof Karl Atkin (Department of Health Sciences, University of York) and held at the University of York aimed to start a dialogue to begin to address these issues. The Meeting was a truly interdisciplinary gathering exploring the broader legacy of Thalidomide. It brought together Thalidomide survivors, historians, scientists, clinicians and social scientists to explore what lessons can be learnt from the history and use of the drug, its impact and ongoing consequences today; and how this knowledge can benefit Thalidomide survivors and others with rare impairments.

Legacy of Thalidomide Meeting

The meeting had three sessions each highlighting different perspectives: historical, contemporary and personal. Professor Karl Atkin, Head of the Department of Health Sciences at the University of York, opened the day. He remarked on the importance of understanding the life course when making sense of long-term conditions and in particular, how ageing with a disability creates specific disadvantages which need to be addressed.

The historical perspectives session began with a joint presentation by Dr Ruth Blue, (Secretary of the Thalidomide Society and Curator at the Wellcome Library) and Mr Brian Payne (Trustee of the Thalidomide Society; <http://www.thalidomidesociety.org/>). In their talk - *The thalidomide story: archives and voices* - they outlined the history of the Thalidomide Society and gave an overview of the practical work they are doing to conserve the history and advise researchers and the media. They also highlighted the wealth of Thalidomide related reports, papers, photographs and films, held by the Wellcome Library

(<http://wellcomelibrary.org/>). The archive also holds oral history recordings from Thalidomide survivors and will soon hold recordings of parents who took the drug.

Dr Julie Parle, (Honorary Associate Professor in History, School of Social Sciences, University of KwaZulu-Natal, South Africa) a UK-born Thalidomide Survivor, gave a fascinating presentation on the research she and other historians have been doing on the 'hidden histories' of thalidomide's distribution, impact and use in African countries since the 1960s (Klausen and Parle, 2015). Her talk showed that Thalidomide has many 'shadow' histories around the world, even where it has not been proven to have directly affected mothers and babies, and how some Thalidomide survivors are themselves now piecing these histories together, bit by bit. She argued that more archives need to be opened to researchers in pursuit of such histories.

The session concluded with a presentation about *Historic photographs for engagement and outreach: experiences from the Global Health Histories project* by Dr Alex Medcalf (Outreach Historian, Centre for Global Health Histories, Department of History, University of York; www.york.ac.uk/history/global-health-histories/). This project involves using visual images to tell a historical story. He highlighted some of the challenges and complexities they have faced in the project, in particular, the ethics of displaying difficult and sensitive material, and the importance of using the images to assist the argument or provoke additional questions.

The contemporary perspective session was opened by Dr Neil Vargesson, (Senior Lecturer, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen). In his presentation - *Thalidomide: mechanisms of action and current challenges* – he gave an overview of current opinion on the drug's mechanisms, in embryos and in adults (Vargesson, 2015). The drug's action on blood vessel formation, its ability to induce cell death and interact with *Cereblon* are widely accepted as mechanisms of the drug's action. Indeed, he described how the drug's actions on blood vessels can result in a range of limb damage (Vargesson, 2009; Vargesson, 2015; Vargesson and Hootnick, In Press). He also described the advances his team has made in finding a 'safe' form of the drug, retaining the clinical benefits but without the side-effect of embryonic damage (Beedie et al., 2016; Beedie et al. In Press). This is extremely relevant today as sadly new generations of Thalidomide children have been born in recent decades in Brazil as the original drug is used to treat a form of Leprosy (Schuler-Faccini et al., 2007; Vargesson, 2013; Vianna et al., 2011).

The contemporary health of Thalidomide survivors in Sweden was discussed by Dr Shadi Ghassemi Jahani (Consultant Orthopaedic Surgeon, Institute of Clinical Sciences, University of Gothenburg, Sweden). Dr Ghassemi Jahani has been researching the orthopaedic problems experienced by Thalidomide survivors in Sweden as they age (Ghassemi Jahani et al., 2014). She set out the findings from her work on osteoarthritis and cervical spine deterioration (Ghassemi Jahani et al., 2016) and then went on to discuss her recent work on Health related quality of life. Her research showed that Thalidomide survivors have significantly lower physical health related quality of life compared with the general population.

Ms Liz Newbronner (PhD student, Department of Health Sciences, University of York) then described her research on the contemporary health of Thalidomide survivors in the UK. Despite the drug being distributed in 48 countries, little research into the health of

Thalidomide survivors as they age has been undertaken and the research that has been carried out is limited to just seven countries – Australia (Jankelowitz et al., 2013), Canada (Vermette and Benegabi, 2013), Germany (Peters et al., 2015), Ireland (O’Carroll et al., 2011), Japan (Shiga et al., 2015), Sweden (Ghassami Jahani et al., 2016) and the UK (Nicotra et al., 2016). Findings from a new national health and wellbeing survey of UK Thalidomide survivors (Newbronner and Baxter, 2016), undertaken for the Thalidomide Trust (<http://www.thalidomidetrust.org/>) were discussed. The data shows that the health of Thalidomide survivors is declining more rapidly than that of their peers in the general population. Whilst this experience is similar in many ways to other people with early onset disability, there are some distinctive aspects and pertinent wider lessons for health and care services. In particular, the complex nature of Thalidomide damage and the implications of comorbidities, both of which call for a strongly collaborative approach between clinicians and Thalidomide survivors.

In the final session of the day, three UK Thalidomide survivors gave their personal reflections on living and ageing with Thalidomide-induced damage. They highlighted the legacy of learning for Thalidomide survivors across the world, other people with rare impairments (especially limb difference), and the clinicians and services that support them. Geoff Adams-Spink (Deputy Chair, European Dysmelia Reference Information Centre; <http://www.dysnet.org/>), discussed the power of networking between Thalidomide survivors and others with limb difference. He emphasised the scope to use networking to address contemporary issues such as the need for peer support, the development of ‘workarounds’ to support everyday tasks, and improved access to specialist health services. Mr Rowland Bareham (Chairman, Thalidomide Trust National Advisory Council) focused on the experiences of Thalidomide survivors with hearing damage. Around a third of Thalidomide survivors have total or partial hearing loss and this ‘hidden’ group of survivors often experience higher levels of poorer mental wellbeing. The day was closed by Dr Craig Millward (Member, Thalidomide Trust National Advisory Council) who spoke movingly about finding out as a young adult that his disabilities had been caused by Thalidomide, and how health problems in middle age had lead him into greater involvement with the Thalidomide community.

Conclusions

The meeting showed that there is still much to learn from Thalidomide, both from its complex history and its impact on peoples’ lives today. For Thalidomide survivors, the original impairments caused by the drug are being compounded by the consequences of a lifetime of living with a rare disability, and early on-set age related health problems. Their health and functioning is changing, and this has profound implications for their quality of life and need for health and social care services. Clinicians and healthcare services often fail to understand the complex nature of Thalidomide damage, nor do they always recognise the self-management knowledge Thalidomide survivors have. It is vital that both these issues are addressed in research, and in clinical practice if Thalidomide survivors are to ‘age well’. Furthermore, the experience of Thalidomide survivors provides lessons for supporting other people with rare impairments. In particular, there is a need for a flexible response which recognises a person’s active engagement with their condition and is sensitive to the consequences of the life course. Finally, the meeting was an important reminder of the continued need for research into drug safety and for pharmacovigilance.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

Acknowledgements

The meeting was funded by the Centre for Chronic Diseases and Disorders at the University of York, which is supported by the Wellcome Trust.

For Peer Review

References

Beedie SL, Rore HM, Barnett S, Chau CH, Luo W, Greig NH, Figg WD, Vargesson N. 2016. In vivo screening and discovery of novel candidate thalidomide analogs in the zebrafish embryo and chicken embryo model systems. *Oncotarget* 7(22):33237-33245.

Beedie SL, Diamond AJ, Fraga LR, Figg WD, Vargesson N. In Press. Vertebrate embryos as tools for anti-angiogenic drug screening and function. *Reprod Toxicol*. In Press <http://dx.doi.org/10.1016/j.reprotox.2016.11.013>

Ghassemi Jahani SA, Danielsson B, Karlsson J, Danielsson AJ. 2014. Long-term follow-up of thalidomide embryopathy: malformations and development of osteoarthritis in the lower extremities and evaluation of upper extremity function. *Journal of Child Orthopaedics* 8:423-433.

Ghassemi Jahani SA, Danielsson A, Ab-Fawaz R, Hebelka H, Danielson B, Brisby H. 2016. Degenerative Changes in the Cervical Spine Are More Common in Middle-Aged Individuals with Thalidomide Embryopathy than in Healthy Controls. *PLoS ONE* 11(5): e0155493. doi:10.1371/journal.pone.0155493

Honoshita F. (2015). Report on the International Symposium on Thalidomide Embryopathy. http://www.thalidomide-embryopathy.com/common/data/pdf/sympo_report_160307_en.pdf

Jankelowitz SK, Spies JM, Burke D. 2013. Late-onset neurological symptoms in thalidomide-exposed subjects: A study of an Australasian cohort. *Eur J Neurol* 20(3):509-514.

Klausen S, Parle J. 2015. Are we going to stand by and let these children come into the world?: The impact of the ‘thalidomide disaster’ in South Africa, 1960-1975. *J South Afr Studies* 41(4):735-752.

Lenz W. 1962. Thalidomide and congenital abnormalities. *Lancet* 1:271–272.

McBride W. 1961. Thalidomide and congenital malformations. *Lancet* 1:358

Newbronner E, Baxter M. 2016. *Changing Lives – The Health and Wellbeing of Thalidomide Survivors in Middle Age*. <http://www.thalidomidetrust.org/wp-content/uploads/2014/01/HW-Survey-2015-FINAL-REPORT-20-May-20161.pdf>

Nicotra A, Newman C, Johnson M, Eremin O, Friede T, and Malik O. 2016. Peripheral Nerve Dysfunction in Middle-Aged Subjects Born with Thalidomide Embryopathy. *PLoS ONE* 11(4): e0152902. doi:10.1371/journal.pone.0152902

O'Carroll A, O'Reilly F, Whitford DL. 2011. 'What has happened to people affected by thalidomide 50 years on?' *Ir J Med Sci* 180(2):475-478.

Peters KM, Albus C, Lungen M, Niecke A, Pfaff H, Samel C. 2015. *Damage to Health, Psychosocial Disorders and Care Requirements of Thalidomide Victims in North Rhine Westphalia from a Long Term Perspective*. Federal Health Centre North Rhine Westphalia, Cologne.

Schuler-Faccini L, Soares RC, de Sousa AC, Maximo C, Luna E, Schwartz IV, Waldman C, Castilla EE. 2007. New cases of thalidomide embryopathy in Brazil. *Birth Defects Res A* 79:671-672.

Shiga T, Shimbo T, Yoshizwa A. 2015. Multicentre Investigation of Lifestyle-Related Diseases and Visceral Disorders in Thalidomide Embryopathy at around 50 years of age. *Birth Defects Res A* 103:787-793.

Smithells RW, Newman CG. 1992. Recognition of thalidomide defects. *J Med Genet* 29:716-723.

Vargesson N. 2009. Thalidomide-induced limb defects: resolving a 50-year-old puzzle. *BioEssays* 31:1327-1336.

Vargesson N. 2013. Thalidomide embryopathy: an enigmatic challenge. *ISRN Dev Biol*. Article ID 241016. <http://dx.doi.org/10.1155/2013/241016>

Vargesson N. 2015. Thalidomide-induced teratogenesis: history and mechanisms. *Birth Defects Res C: Embryo Today: Reviews* 105:140–156.

Vargesson N, Hootnick DR. In Press. Arterial dysgenesis and limb defects: Clinical and experimental examples. *Reprod Toxicol*. In Press <http://dx.doi.org/10.1016/j.reprotox.2016.10.005>

Vermette N, Benegabi M. 2013. Study on the current living conditions of Canadian Thalidomide survivors and projections for the future. *Thalidomide Victims Association of Canada*. http://www.thalidomide.ca/actualites_1827_en/

Vianna FSL, Lopez-Camelo JS, Leite JC, Sanseverino MT, Dutra Mda G, Castilla EE, Schuler-Faccini L. 2011. Epidemiological surveillance of birth defects compatible with thalidomide embryopathy in Brazil. *PLoS ONE* 6(7):e21735. doi: 10.1371/journal.pone.0021735

World Health Organisation (2014). *Thalidomide Embryopathy - Report of a meeting of experts*. www.who-umc.org/graphics/28280.pdf